REMARKS

Claims

Claims 1–16 are pending. Claims 17–18 are added by this paper.

Amendments

Amended claims 1 and 4 are supported by the disclosure contained in, for example, page 8, lines 17–19. It is submitted that the claim amendments do not add new matter.

New independent claim 17 recites the compounds of the instant invention, and is supported in part, by the disclosure contained in the Examples. Support for dependent claim 18 can be found in, for example, the disclosure contained in page 6, lines 21–26 and page 10, lines 31–33 of the originally filed specification. Entry thereof is kindly requested.

Rejection under 35 U.S.C. §102(b)

Claims 1 and 2 stand rejected under §102(b) as allegedly being anticipated by the teachings of Crofford (*Arthritis and Rheumatism*, vol. 43, pp. 1891-1896, 2000). This rejection is respectfully traversed.

It is respectfully submitted that the rejection is moot in view of the amendments. Crofford et al. is only directed to the use of cox-2 inhibitors for the treatment of osteoarthritis and rheumatoid arthritis. See, Tables 2 and 3 and the "Case Reports" section of the Crofford et al. The cited reference fails to teach or disclose all the elements of Applicants' claims. For example, Crofford is absolutely silent with respect to EP_2 receptor inhibition. See, amended claim 1. Absent such disclosure, there can be no anticipation. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103(a)

The contention that claims 1–16 are rendered obvious and thus unpatentable under 35 U.S.C. §103(a) over Breyer, Hizaki and Narumiya (primary references) in view of Norel and Nobel et al. (secondary references) is respectfully traversed.

The Office Action contends that based on Breyer, Narumiya and Hizaki's (primary references') disclosure of EP_2 inhibition and in view of the teachings of Norel, Nobel, and the art knowledge of Cox-2 inhibition (secondary references), "it would have been obvious to one of ordinary skill in the art to employ AH6809 and/or celecoxib in a method of controlling fertility or

impairing cumulus expansion and oocyte maturation." See, the last paragraph at page 8 of the Office Action. The Examiner proceeds to contend that "it is known that inhibition of EP_2 activation and Cox-2 would lead to impair ovulation, fertilization, implantation, and abortive expansion of the cumulus." (Emphasis added).

As discussed previously in Applicants' Reply filed February 20, 2007, neither the primary nor the secondary reference discloses *a combination of EP_2 receptor antagonism and cox-2 inhibition*. The Examiner is cordially invited to review Applicants' analysis of the cited references filed with the previous Reply. Breyer is drawn to EP_2 receptor knockout mice and fails to mention of EP_2 antagonists or a combination of such antagonists with cox-2 inhibitors. Like Breyer, Hizaki discloses the physiological traits of an EP_2 receptor knockout mouse. Hizaki is also silent as to the use of a pharmacological intervention (i.e., antagonists) against the particular receptor subtype(s), and whether such antagonists can be used with cox-2 inhibitors in a manner described in Applicants claims. Narumiya's article provides an overview of prostanoids and their activity. It is disclosed that the receptor family comprises TP, IP, EP, FP, and DP receptors, which are specific for Tx, PGI, PGE, PGF, and PGD ligands, respectively. With respect to cox-2 receptors, Narumiya cites the Hizaki publication, discussed *supra*, and states that "the EP_2 receptor and COX-2 are induced in the cumulus in response to gonadotropins." See, ¶2 at page 1217 of Narumiya. However, there is no mention of the physiological effect elicited by cox-2 inhibition, including whether EP_2 antagonism along with cox-2 inhibition will render the claimed physiological effect.

The additionally cited secondary references of Norel and/or Noble either solely or in combination fail to rectify the above-cited limitations of the primary references. For example, the secondary reference of Norel teaches the use of an EP_2 antagonists in bronchial relaxation and Noble's disclosure is drawn to the use of cox-2 inhibitors for their anti-platelet activity, anti-arthritic effects, and in the treatment of CHD, diabetes, dehydration or aging. The secondary references offer no guidance or suggestion regarding the use of the claimed agents for inhibiting cumulus formation and oocyte maturation. Moreover, neither Norel nor Noble provides any guidance or suggestion with respect to EP_2 receptor antagonism and a cox-2 inhibition, especially in relation to the claimed biological effects. Therefore, the claimed invention is wholly unobvious over the cited primary and/or secondary references.

Overall, the cited references, either solely or in combination, fail to disclose a method for inhibiting cumulus formation and oocyte maturation comprising antagonizing an EP_2 receptor and inhibiting cox-2. Moreover, since the primary references make no mention of cox-2

inhibition or a mode of pharmacological intervention comprising administering a cox-2 inhibitor together with an EP_2 antagonist, the cited references, even at their broadest possible interpretation, fail to render obvious what is claimed by the instant application. The Office Action contends that one of ordinary skill in the art would have been motivated to employ AH6809 (an EP_1/EP_2 antagonist) and celecoxib (a COX-2 inhibitor) in a method of controlling fertility or impairing cumulus expansion and oocyte maturation because the primary references teach that EP_2 receptor disruption and COX-2 inhibition can inhibit ovulation. But, as discussed *supra*, clearly this is not the case.

The Office Action thus has failed to meet the basic criteria for *prima facie* case of obviousness. As such, all the rejections under 35 U.S.C. §103(b) must be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claim 1 stands rejected under 35 U.S.C. §112, first paragraph as allegedly being non-enabled. Applicants respectfully traverse the rejection.

The Office Action at page 2 alleges that the instant specification "while being enabling for antagonizing the EP_2 receptor by EP_2 antagonist does not reasonably provide enablement for the use of other antagonizing method." The Office Action does not explain what these "other antagonizing methods" constitute. If the Examiner is referring to complete knockout of EP_2 receptor (as described in the Breyer and/or Hizaki references, discussed *supra*) then the Examiner is courteously requested to point to relevant passages in the cited Breyer and Hizaki references which establish this fact.

At the outset, it is submitted that insofar as the term "modalities" is not used in the instant specification, any contention on non-enablement based on its alleged use, without an express definition of such term, is unsupported. According to the medical dictionary, "modality" is defined as "a therapeutic method or agent, such as surgery, chemotherapy, or electrotherapy that involves the physical treatment of a disorder." This definition is relied upon to rebut the PTO's allegation that the scope of the claims is non-enabled.

With respect to the PTO's reliance on *In re Wands*, Applicants traverse the following applies:

1. State of art and level of the skilled worker

Based on the above-cited Breyer, Hizaki and Narumiya references, and further in view of Applicants' own specification and the references cited therein, it is courteously submitted that

knowledge of EP_2 receptor molecules, including methods for *in vitro* and/or *in vivo* modulation thereof, was conventionally appreciated in the art as of the filing date of the instant application. Given this replete state of the art, the knowledge/skill available to an average biologist involved in the assessment of the activity of the claimed receptor molecules in a manner that is commensurate with the instant application, is also high.

2. Alleged lack of working examples

Applicants' specification and the art knowledge of EP_2 receptor and Cox-2 proteins provide express guidance with respect to the structure of the representative molecules having antagonistic and/or inhibitory activity on such proteins, including methods for using such molecules for achieving the claimed biological effects. In the paragraphs bridging pages 7, line 29 to page 8, line 10, Applicants' specification provides a list of patent publications and literature references which disclose molecules having the claimed EP_2 receptor antagonistic activity. For example, Nagao (US 2001005760) discloses a list of naphthyloxyacetic acid derivatives which serve as EP_2 receptor antagonists. See, "Pharmacological Activities" section at page 27 of Nagao et al. Ortho-substituted aromatic compounds which serve as EP_2 antagonists are discussed in Park et al. (EP752421), which the present application incorporates by reference in its entirety. Furthermore, compounds having EP_2 antagonistic activity and their use in stopping hair growth is described in the incorporated publication by Bernard et al (EP1175889). In a similar manner, in the paragraphs bridging pages 10, lines 5–25, Applicants' specification provides a list of patent publications and literature references which disclose molecules having the claimed cox-2 inhibitory activity. Applicants' specification also provides a detailed disclosure pertaining to the use of such compounds. For example, claimed embodiments drawn to "selective" and/or "highly selective" compounds are disclosed with the preferred dose ranges. See, the paragraphs bridging pages 19 and 20 of the originally-filed specification. As such, the allegation that "only a limited number of examples are set forth" is not supported on the record.

3. Undue experimentation

With respect to the quantity of experimentation needed to assess the physiological activity of the claimed compounds, the Office Action at pages 3–4 alleges that "the pharmaceutical art is unpredictable" and that the claims "read on all compounds or modalities [whose] physiological activity must be experimentally discovered by the skilled artisan." Applicants disagree.

The Office Action fails to provide a single reference on which to base this contention. As clearly and succinctly stated by the court in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> As a matter of Patent Office practice, then a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken in compliance with the enabling requirement of the first paragraph of §112, **unless** there is reason to doubt the objective truth of statements contained therein relied on for enabling support. (emphasis in original)

See also *In re Bundy*, 209 USPQ 48 (CPA 1981). Thus, in the absence of evidence which demonstrates otherwise, the claims must be taken to satisfy the requirements of 35 U.S.C. §112, first paragraph. Here, the focus is on the physiological effect of EP_2 receptor antagonism and COX-2 inhibition. The rationale for the use of the claimed inhibitors is clearly described in the specification by the way of scientific references and experimental data. See, the disclosure contained in the paragraphs bridging page 12, line 13 to page 13, line 7 of the instant specification and the disclosure contained in the Examples.

In light of this detailed disclosure, to assert a lack of enablement, the courts have placed the burden on the PTO to show otherwise. It is courteously submitted that the Patent Office has not presented any evidence to refute the findings or the conclusions made in the specification or the supporting publications. In addition, no evidence has been presented to support the contention that the claimed molecules could not be used, in a manner that is commensurate with Applicants' claimed invention. Only unsupported allegations and conclusions regarding the "complexity" and "unpredictability" of the "state of the art" are provided to support the contention. These allegations are especially weak in the face of the showing that the field of EP_2/Cox-2 molecules, modulators thereof (i.e., agonists and antagonists) and reagents/assay techniques for the measurement of the activity of such modulators were all conventionally appreciated in the art well before the filing date of the instant application. Furthermore, given the rapid technological progress made in the post-genomic era, a skilled artisan could utilize Hizaki and/or Breyer's protocols for the study of the activity of EP_2 receptor antagonists (discussed *supra*) in combination with the aforementioned cox-2 inhibitors. This process would constitute nothing more than routine work to those in the art. As clearly established in *Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998):

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or

> if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. (Emphasis added)

Thus, based on routine nature of biological assays and the disclosure provided by Applicants' own specification and the art knowledge of the *in vivo* role(s) of the EP_2 and Cox-2 receptor molecules, it is hereby submitted that the subject matter of Applicants' claims are fully enabled.

4. Amount of guidance or direction provided

The Office Action at page 4 contends that "Absent the small genus of compounds herein recited, the instant invention is silent as to making or using...macromolecules such as proteins, peptides, and genes." This contention is respectfully traversed.

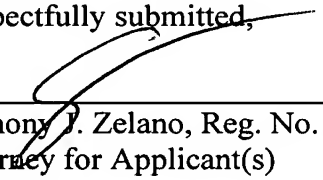
By "macromolecules" it is assumed that the Office Action is referring to antibody molecules, peptides, and/or siRNA, which may be used to selectively target and thus modulate the expression/function of the claimed EP_2 receptor molecules. Insofar as such molecules were known before the filing date of the instant application, it is respectfully submitted that the use of such "macromolecules" is clearly commensurate with Applicants' claims. For example, a PUBMED search with the term "EP2 receptor" AND "antibody" reveals 10 publications which were available to the skilled worker before the earliest priority date of the instant application (6/26/2002). Additionally, in view of the fact that techniques for small-interfering RNA (siRNA) were well-established and the nucleotide sequence for the claimed receptor molecule was well-known in the art, a skilled artisan, if desired, could routinely employ siRNA-mediated modulation of the claimed EP_2 receptor activity. Other chemical/genetic approaches could also be routinely employed. Again, it is respectfully submitted that the Office Action does not provide any evidence that the claimed molecules could not be used, in a manner that is commensurate with Applicants' claims.

In view of the above remarks, it is respectfully submitted that Applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is routine in the art. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,



Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: **SCH-1985**

Date: September 14, 2007